REMARKS

A check for the fees for a three month extension of time and for filing an RCE accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A change of address for the undersigned accompanies this response.

Claims 45, 46, 62, 70, 78, 94, 96-100 are pending in this application. Claims 45 and 62 are amended herein for clarity. Claims 96 and 97, which are added, find basis in the specification as originally, filed. For example, basis can be found in the Table spanning pages 53-71. Claim 45 also is amended to remove reference to AAV-5. This is not to be construed as an admission that AAV-5 rep mutants cannot be prepared and used as provided in the instant application, but in order to advance prosecution of the application.

An attachment showing the conservation among the sequences of the REP proteins of AAV-2, AAV-3, AAV-3b, AAV-4, AAV-6 and AAV-7. In this instance, * means that the amino acid at the locus is different among two or more serotypes (generally 80% share the same residue); # indicates that the differences are conservative substitutions. Keeping this in mind, the attachments visually depict how similar and conserved the proteins are among the AAV serotypes as claimed. Furthermore, when the substitutions are made as claimed, the proteins are, if anything, even **more** similar.

Traversal of the Restriction Requirement and Election of Species

. As discussed below and in the previous responses, it respectfully is submitted that the Examiner is not following the rules for restriction of claims to nucleic acid molecules nor for election of species. Claim 45 is a genus claim and hence is a linking claim.

> 45. A nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity, wherein increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host cell of virus, in its genome, encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene.

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies particular amino acid replacements in the mutant Rep protein:

> A nucleic acid molecule of claim 45, comprising mutations at one or more of residues, whereby the activity of the mutant Rep protein is increased as assessed by rAAV production compared to the native Rep protein, wherein:
>
> the mutations comprise replacements of codons encoding native amino acid residue(s) selected from among: T by N at position 350 of (SEQ

> ID No. 747); T by I at position 462 of SEQ ID No. 747); P by R or L or Y at position 497 of SEQ ID No. 747; T by N at position 517 of SEQ ID No. 747; G by D or S at position 598 of SEQ ID No. 747 or V by P at position 600 of SEQ ID No. 747 or the same replacements of the corresponding residues in the other serotypes;
>
> residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of SEQ ID No. 746 of the AAV-2 genome; and
>
> the listed residues reference their positions in wildtype AAV-2 nucleic acid molecules and the encoded proteins set forth in SEQ ID Nos. 746 and 747, respectively.

Comparison of claim 45 and claim 62 shows that claim 45 encompasses a nucleic acid molecule encoding a mutant Rep protein of increased activity where the increased activity is *manifested as an increased titer of virus upon introduction and replication in a host cell of virus containing the nucleic acid molecule encoding the mutant Rep protein(s)*. Claim 62 is directed to a nucleic acid molecule of claim 45 that includes the specified amino acid replacements in the Rep protein. Thus, claim 45 is directed to a genus of nucleic acid molecules encoding a mutant Rep protein with increased activity as assessed by increased AAV titer, and claim 62 is directed to species of nucleic acid molecules encoding Rep protein with increased activity that have the mutations as specified.

Thus, claim 45 and claim 62 are related as genus/species. Genus claims linking species are linking claims. *See* MPEP §809.03. Thus, claim 45 is a linking claim As noted above, linking claims must be examined with the elected species. MPEP §809. Furthermore, if the linking claims are found allowable, then all species linked thereby must be rejoined.

Restriction to a single molecule

Restrictions to single nucleotide sequences are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, but the Commissioner has decided sua sponte to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP '803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patently indistinct from the selected sequences will also be examined. **Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.** [emphasis added]

Accordingly, in this instance, the Examiner allegedly has only permitted examination of a single sequence, not the reasonable number, as set forth in MPEP §803.04. Further, as discussed previously and below, the claims are directed to nucleic acids encoding a single protein and to serotype variations. Nucleotide sequences encoding the same protein are not considered independent inventions and will continue to be examined together.

The claimed species cover mutations in the same genes and proteins encoded by the overlapping gene

The subject matter of the claims is directed to nucleic acid molecules encoding modifications (8) of AV Rep protein, and virus and cells containing such nucleic acid molecules. As set forth in MPEP §803.04, nucleotide molecules encoding the same protein will be examined together. The mutations at the specified positions all in the Rep proteins, which are encoded by overlapping nucleic acid.. The types of mutation (insertion, deletion or replacement) are all mutations in the same gene, the gene the encodes the Rep proteins. Thus, because the claimed mutations are all positions and types of mutations in the same protein, they should be examined together.

The types of AAV Rep protein, Rep 78, Rep68, Rep52 and Rep 40, all are encoded within the nucleic acid molecules which include overlapping open reading frames. As described in the specification, Rep 78 is encoded by nucleotides 321-2186, Rep 68 is encoded by nucleotides 321-1906, Rep 52 is encoded by nucleotides 993-2186, and Rep 40 is encoded by nucleotides 993-1906 and 228-2252 of AAV (see for example, at page 31). Thus, the sequence of nucleotides encoding Rep 78 encompasses the sequences of nucleotides encoding Rep 68, Rep 52 and Rep 40. Hence, a search of nucleic acid molecules encoding one type of Rep protein (e.g., Rep 78) is the same search as for nucleic acid molecules encoding all of the Rep proteins. Further a single search for AAV Rep protein will reveal any molecules encoding the specifically claimed in claim 62. Based upon mutations to particular loci, there only are 6 different mutant loci. One search of the gene should cover all of the mutations.

Applicant also respectfully submits that AAV serotypes, AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5 or AAV6 are highly conserved. The Rep proteins among these serotypes seven highly conserved molecules encoding the AAV Rep protein. Furthermore, the Rep proteins of the serotypes of AAV represent allelic variants.

Linking claim

Even if restriction to a single specific sequence of nucleotides is permissible, claim 45 and dependent claims, as originally filed, and as presently, pending is a generic claim and as such, is a linking claims. Linking claims must be examined with an elected group. Claim 45 is directed to nucleic acid molecules encoding REP protein mutants that result in increased titer off AAV encoding such proteins. Thus far in prosecution, the Examiner has not identified any art pertinent to claim 45. Applicant and the undersigned, who have done extensive searching, are unaware of any art disclosing REP protein mutations that result in increased titer.

As noted claim 45 is a linking claim linking dependent claims, directed to nucleic acid molecules encoding AAV Rep proteins that result in increased titer. According to MPEP '809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on 1) specifying the linking claims; and 2) examining the linking claims with the elected group. The linking claims must be examined with the elected group, and the Restriction Requirement must be conditioned on allowability of the linking claims. If the linking claims are deemed allowable, then the Restriction Requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined.

In this instance, the Examiner failed to specify the linking claim and it is unclear whether it has been examined. If claims 45 is deemed allowable the restriction requirement and election of species dividing the pending claims must be withdrawn.

Election of species is for search purposes

Applicant has elected for search purposes species of nucleic acid molecules encoding a mutant rep protein where the mutation is a replacement of a T by N at position 350 in the Rep78 protein, the AAV serotype is AAV-2 and the mutant has increased activity as compared to the native protein.

Applicant respectfully submits, however, that an election of species is for search purposes. The Examiner should search the species and if no art is found then a second species should be searched until art is found or until a reasonable number of species is searched. In this instance, no art pertinent to the elected species has been identified. Accordingly, searching should have proceeded with additional species.

Furthermore, generic claim 45 is amenable to searching. Searching for Rep Protein from AAV, would not constitute an enormous burden as urged by the Examiner. The

applicant and undersigned have conducted such searches and have not identified any disclosure of disclosed REP mutant polypeptides nor any disclosures providing REP mutant polypeptides that result in increased titer of viruses that express such polypeptides.

Finally, it is noted that the originally drafted Restriction Requirement set forth 28 groups (now somewhat reduced) and 6 or 8 species for each group. If only a single so-called species is prosecuted with each group, then over 150 applications must be filed to cover the subject matter of this application, which is directed to mutations in one gene in a well-characterized small virus (AAV), when virtually all of the subject matter can be searched by searching for the protein and variations thereof. The Office is reminded that:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Hence, if this election of species is maintained (as well as the restriction requirement), applicant can file more than 100 applications to each so-called species, and obviousness-type double patenting cannot be held.

Also, it is noted that realistically, it is cost prohibitive for applicant to file and prosecute 150 applications. In essence, a restriction requirement (since the election of species is being treated as such), will unduly limit the claims to one molecule, where the disclosure shows 1) that one can mutate the REP protein such that viral titer is increased, which was heretofore not known; 2) numerous examples of such mutations, and 3) methods to obtain other such mutations. Thus, if claims to a single species are only examined, one of skill in the art can practice what is disclosed in the application, yet avoid infringement.

Objection to the Specification

The specification previously has been amended to correct the inadvertent grammatical error noted by the Examiner. Applicant requests deferral of any remaining issues until the other outstanding issues are resolved.

Applicant, however, notes, that the recitation of amino acids on page 17 with reference to the ClustalW program is not a definition of hydrophobic amino acids, but a recitation of the parameters employed in the program. The recitation of "hydrophobic" preceding a list of hydrophilic amino acids is an obvious typographical error. A printout from the ClustalW program shows that the listed amino acids DEGKNPQRS are the protein sequence parameters identified as hydrophilic residues. The reference paragraph in the specification sets for the parameters employed.

Claim Objections

Claim 62 is amended to correct the informalities noted by the Examiner. The reference to the SEQ ID No. 747 is a reference to the wild-type AAV-2 sequence; the claim recites that the referenced residue is replaced. SEQ ID No. 746 does set forth the sequence of the entire genome. The first open reading frame, which encompasses all or part of the REP proteins is translated in SEQ ID No. 746. The claim recites "residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of SEQ ID No. 746 of the AAV-2 genome," so it is clear where in the genome the Rep proteins begin.

The rejection of claims 62, 70, 78, 94 and 95 under 35 U.S.C. §112, second paragraph

Claims 45, 62, 70, 78, 94 and 95 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the recitation of "residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of SEQ ID No. 746 of the AAV-2 genome" because the skilled artisan could think that SEQ ID No. 746 sets forth the sequence of the entire genome. No reason is given for rejection of claim 45 and claims dependent thereon. This rejection is respectfully traversed.

Relevant law

If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); *See, also, Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. It is unnecessary and unduly limiting to recite steps routine to those of skill in the art at the time the application was filed, such as wash steps and release of a bound polypeptide prior to analysis. A claim is not required to be a recipe, but rather defines the metes and bounds of the claimed subject matter. There is no requirement to include routine steps, which may be optional or performed in a variety of different ways.

Claims

Claim 62 is directed to a nucleic acid molecule that encodes an AAV Rep protein, comprising mutations at one or more of residues, whereby the activity of the mutant Rep protein is increased as assessed by rAAV production compared to the native Rep protein. The mutations are replacements of codons encoding native amino acid residue(s) selected from among: T by N at position 350 of SEQ ID No. 747; T by I at position 462 of SEQ ID No. 747; P by R or L or Y at position 497 of SEQ ID No. 747; T by N at position 517 of SEQ ID No. 747; G by D or S at position 598 of SEQ ID No. 747; or V by P at position 600 of SEQ ID No. 747-or the same replacements of the corresponding residues in the other serotypes. Residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of SEQ ID No. 746 of the AAV-2 genome; and the listed residues reference their positions in wildtype AAV-2 nucleic acid and proteins set forth in SEQ ID Nos. 746 and 747, respectively. Dependent claim 94 recites that the protein is Rep78, Rep68, Rep52 or Rep48 and references the particular sequence IDs and also recites that the corresponding proteins from the other serotypes are included.

Analysis

The specification teaches the locus of each Rep protein in the AAV genome. For example, at page 31, the specification states that Rep 78 is encoded by nucleotides 321-2,186; Rep68 is encoded by nucleotides 321-2186 and 2228-2252; Rep 52 is encoded by nucleotides 993-2,186; and Rep 40 is encoded by amino acids 993-1906 of wildtype AAV. It is clear that SEQ ID No. 746 sets for residues 1-4675 of the AAV-2 genome the amino acids from the first open reading frame encoded thereby are set forth in SEQ ID Nos. 746 and 747. Figure 3 sets for the amino acid sequences of Rep proteins from 7 different serotypes.

Claim 62 recites the nucleic acid molecule encodes a Rep protein with one or more mutations and then the loci of such mutations, referencing SEQ ID Nos. 746 and 747. Reading the claim in light of the specification, one of skill in the art would readily be able to deduce the sequence of the nucleic acid molecule. The specification describes the positions

of each of the proteins as encoded by the nucleic acid molecule set forth in SEQ ID No 746 and SEQ ID No. 746 sets forth the nucleic acid sequence encoding all of the Rep proteins (*i.e.*, Rep 78 is encoded by nucleotides 321-2,168, Rep 40 is encoded by amino acids 993-1906 etc.). Figure 3 aligns the Rep 78 proteins from seven serotypes and identifies the hit positions, and the specification references the sequences of the serotypes (SEQ ID NOs. 736-748) from which the corresponding nucleic acid molecules from the seven serotypes can be determined. Hence one of skill in the art by following the instructions in the specification and claim can identify which nucleotides encode each protein and the loci for each of the mutations therein.

THE REJECTION OF CLAIMS 45, 46, 62, 94 AND 95 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

35 U.S.C. §112, first paragraph - Written description

Claims 45, 46, 62, 94 and 95 are rejection under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because it is alleged that the specification fails to demonstrate that applicant had possession of the nucleic acid molecules encoding the mutant Rep proteins from serotypes AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5 and AAV-6. The Examiner urges:

> Referring to Figure 3A, position 350 of AAV-2 is indeed a T residue. In five of the other six serotypes, this position is occupied by an A. Thus, how could the skilled artisan assume that an A to N mutation in any of these serotypes would have the same activity as the exemplified T to N mutation? There is no assurance that these mutations would have the same type of activity. The mutations identified in the instant application to AAV-2 rep are completely random and bear no reasoning for mutating the particular residues. Thus no structure function relationship exists between the identified mutations and the protein. In essence there is no apparent understanding why, for example the T to N mutation that is exemplified has the effect that it does.
>
> There is no way this method could have identified position 350 is any of the five other serotypes had been used in this screen. As Figure 3A shows, this position is already an alanine in these other serotypes. If indeed this position were so critical, then wild type AAV-1, AAV-3, AAV-3b, AAV-4, and AAV-6 would necessarily have reduced viral titer relative to AAV-2 or AAV-5, as the initial screen to identify "hits" showed that a T to A mutation at position 350 in AAV-2 resulted in a reduced viral titer. The specification does not teach this and there is no fair suggestion of this difference in the prior art. The skilled artisan would have no reason to believe that the mutation to N at position 350 in AAV-2 would correlate to a mutation to N at position 350 or 346 in any other AAV serotype. Thus, the skilled artisan would find no evidence, based on the specification, as filed, that the

inventors were in possession of the full genus of a mutation at position 350 to N in any AAV-serotype.

This rejection is respectfully traversed. The remarks of the Examiner noted above and others are discussed in turn below.

Relevant law

Relevant law

Relevant law and a discussion of the Patent Office Guidelines are set in the previous response of record in this application. Briefly, The Federal Circuit has discussed the application of the written description requirement of the first paragraph of 112 to claims in the field of biotechnology. See University of California v. Eli and Co., 1 19 1559, 43 1398, 1406 (Fed. Cir. 1997). The court explained that:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . a generic statement such as "vertebrate insulin or "mammalian insulin without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also stated that "[a]written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]chemical name, 'of the claimed subject matter sufficient to distinguish it from other materials." at 1567, 43 at 1405. Finally, the court addressed the manner by which a genus of might be described. "A description of a genus of may be achieved by means of a recitation of a representative number of examples defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The Federal Circuit also has addressed the written description requirement in the context of biotechnology-related subject matter in Enzo Biochem. Inc. v. Gen-Probe 296 1316, 63 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that:

> the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' [Emphasis added] at 3

. The court in Enzo adopted its standard from the Written Description Examination Guidelines. 296 at 1324, 63 at 3 (citing the Guidelines), discussed in the previous response. The Guidelines apply to proteins as well as nucleic acid molecules.

The claims

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity. Increased activity of the Rep protein as defined by the specification and claim is "manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene."

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies specific amino acid replacements in an encoded mutant Rep protein, thereby specifying mutations in the encoding nucleic acid molecules and in the corresponding encoded Rep 52 and Rep 40 proteins.

Analysis

First, to satisfy the written description requirement it is not necessary for the application describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that an applicant invented the claimed subject matter. Thus, the fact that the specification does not describe or list all species that have an increased titer by virtue of a particular mutation in a gene is not dispositive of the written description issue. The Enzo court stated that "the written description requirement can be met by that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 'at 63 at 3 (emphasis omitted, bracketed material in original).

In this instance, this standard is met. The specification specifically describes chemical formulae for Rep proteins that exhibit increased titer. The specification describes eight such mutants and provides the formulae for mutant proteins for all loci, including the locus

addressed by the Examiner. Furthermore, the specification provides the sequence of seven serotypes and identifies the mutations as in the corresponding loci. While not conceding that is necessary, as amended, the claims recite the highly related serotypes of AAV. The high conservation of sequence is demonstrated in the attached reproduction of Figures 3A and 3B, but eliminating AAV-5 and noting the differences that represent conservative amino acid differences among the serotypes. Sequence of amino acids encoded amino by the nucleic acids are highly conserved. Furthermore, introduction of the claimed substitutions for increasing titer renders the sequences even **more** similar. One of skill in the art could in view of the disclosure in the specification set forth the sequences of the exemplified Rep mutants for all of the claimed serotypes. Hence there can be no doubt that applicant possessed the claimed species at the time of filing. Furthermore, having exemplified eight mutations and seven different serotypes and also means for producing and testing additional modified Rep proteins and nucleic acid molecules encoding the same, applicant has evidence possession of the genus as claimed (and as claimed prior to amendment).

The Examiner's contention that the specification must provide a description of the location and nature of all the modifications that can be made to generate mutations with increased titer (even at the single locus) is not correct. There is no requirement to disclose every species encompassed by a claimed genus. In this instance, the specification defines structural features and that identify the claimed genus of polypeptides (and hence nucleic acid molecules. Such description includes the sequences of the polypeptides. Hence, the specification does provide the location and nature of modifications in seven serotypes. Furthermore, the specification teaches how to assay and test for increased titer, teaches the locus of eight such mutations and teaches how to generate and screen for any others.

The specification demonstrates that mutations in the Rep protein can result in increased viral titer. Such concept was heretofore unknown. The specification provides a description of mutants that result in increased titer, and provides a method for generating and identifying mutants possess the requisite activity. One of skill in the art using routine methods and the teachings in the specification can clearly identify all of the polypeptides that possess the requisite activity.

Contrary to the Examiner's position, one of skill in the art would conclude that the description in the specification, constitutes a sufficiently detailed, description of identifying characteristics of the claimed subject matter consistent with Enzo (supra). Furthermore, the Examiner has failed to indicate why one of skill in the art, who is in possession of the

polypeptides (and by extension the encoding nucleic acid molecules) as well as all three proteins encoded by the overlapping reading frames, in view of the description in the specification of exemplary species, including Figures 3, and of methods for preparing and testing polypeptides for activity, in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant invented the claimed subject matter. The specification clearly exemplifies mutations in the AAV genome that result in increased viral titer, and teaches in great detail how to generate other such species. The fact that not all members of the genus are disclosed does not demonstrate that one of skill in the art would not recognize that the Applicant invented the claimed subject matter.

Rebuttal to specific remarks of the Examiner

1. Referring to Figure 3A, position 350 of AAV-2 is indeed a T residue. In five of the other six serotypes, this position is occupied by an A. Thus, how could the skilled artisan assume that an A to N mutation in any of these serotypes would have the same activity as the exemplified T to N mutation? There is no assurance that these mutations would have the same type of activity. The mutations identified in the instant application to AAV-2 rep are completely random and bear no reasoning for mutating the particular residues. Thus no structure function relationship exists between the identified mutations and the protein. In essence there is no apparent understanding why, for example the T to N mutation that is exemplified has the effect that it does.

Applicant respectfully disagrees. The identified mutations may have be "random" in that the basis for their effects is not described, but this does not mean that these mutations in the other serotypes, among highly conserved proteins do not have the same effect As is visually evident from Figures 3A and 3B, and attachments A and B, below, the proteins are highly conserved among the serotypes. Further, it does not matter what the starting amino acid, upon replacement with the replacing amino acid the resulting modified polypeptide is even more conserved among the serotypes. Position 350 in the mutant proteins will be an "N" in all serotypes. Furthermore the specification provides assays for testing the resulting nucleic acid molecules in AAV species to assess whether a particular mutation results in increased titer.

The specification demonstrates that modification of nucleic acid including this residue as recited in the claims results upon introduction into the viral genome. The fact that replacement of this residue with N results in increased titer is demonstrated in the specification. As visually depicted and apparent by comparison among the sequences of the other serotypes, the encoded proteins are highly conserved. Applicant clearly had possession

of nucleic acid molecules from any AAV serotype with the modifications as claimed. The claims are not directed to the molecules prior to modification, but with the modifications, and hence with modifications that increase viral titer.

2. There is no way this method could have identified position 350 is any of the five other serotypes had been used in this screen. As Figure 3A shows, this position is already an alanine in these other serotypes. If indeed this position were so critical, then wild type AAV-1, AAV-3, AAV-3b, AAV-4, and AAV-6 would necessarily have reduced viral titer relative to AAV-2 or AAV-5, as the initial screen to identify "hits" showed that a T to A mutation at position 350 in AAV-2 resulted in a reduced viral titer. The specification does not teach this and there is no fair suggestion of this difference in the prior art. The skilled artisan would have no reason to believe that the mutation to N at position 350 in AAV-2 would correlate to a mutation to N at position 350 or 346 in any other AAV serotype. Thus, the skilled artisan would find no evidence, based on the specification, as filed, that the inventors were in possession of the full genus of a mutation at position 350 to N in any AAV-serotype.

Applicant respectfully disagrees. To prepare the modified nucleic acids as claimed, there is no need to perform an alanine screen of these loci. The exemplified loci for modification and the modifications therefor are described. It is not relevant whether or not an Alanine screen would have identified a particular locus if the initial experiment were performed with the starting strain.

3. This then leads to the question; does this mutation in the full-length rep protein, Rep 78 of AAV-2 suggest to the skilled artisan that the inventors were in possession of all of the species of rep, including Rep 68, Rep 52, and Rep 40? Again, the short answer is no. It is understood that the different rep proteins of AAV-2 would possess the same T residue at this position, as the differences between the rep proteins are due to differential promoter use and differential splicing, yet all four proteins use the same reading frame. It is further understood that a T to N mutation in Rep 78 would necessarily lead to a T to N mutation is the other three rep proteins. The question then becomes, would each of the individual rep proteins be expected to individually lead to an increase in viral titer? "Rep 52 and 40, the two minor forms of the Rep proteins, do not bind to ITRs and are dispensable for viral DNA replication and site-specific integration" (page 3, line 7-9). As Rep 52 and Rep 40 apparently play no role in ITR binding, viral replication, or viral integration, the skilled artisan would have no reason to conclude, absent evidence to the contrary, that a mutant form of Rep 52 or Rep 40 would be capable of leading to an increased viral titer. Again, there is no teaching in the specification and no finding in the prior art that would suggest that Rep 52 or Rep 40 would have the activity that leads to the increased viral titer seen in the T to N mutation at position 350 of Rep 78. Thus, the skilled artisan would not have reason to believe the inventors were in possession of the invention as broadly claimed.

Applicant respectfully disagrees. First, it is noted that the instant claims are directed to nucleic acid molecules that encode the Rep proteins, not to the Rep proteins. The claims recite that "a Rep protein that has increased activity, wherein increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host

cell of virus containing, in its genome, the nucleic acid molecule encoding the mutant Rep protein "

The effect claimed is assessed by introducing the nucleic acid molecule into an AAV genome and producing AAV, whereby viral titer increases. Possession of the claimed nucleic acid molecules does not require a knowledge of which of the overlapping encoded proteins is responsible for the effect, but only that if the change is made in the nucleic acid, the resulting viral titer of viruses containing such modification in their genomes is increased. Clearly, for any particular mutation, all of the Rep proteins that include such locus include a modification.

There is nothing in the law that requires a detailed explanation of the mechanism by which a process or work functions to evidence possession. As noted above, the specification exemplifies eight such modifications in the nucleic acid molecules in seven different serotypes, and teaches how to identify other such modifications. This is sufficient disclosure to evidence possession of the claimed genus of nucleic acid molecules.

4. The rejection specifically points out, through analysis of the sequences why the skilled artisan would not be of the opinion that the claimed mutation, T to N at position 350, would result in the same phenotypes in different AAV serotypes. This analysis has in no way been addressed

Applicant respectfully disagrees. The Examiner provides no evidence upon which to base this conclusion. The Examiner cannot take judicial notice of facts outside the record unless such facts are notoriously well-known. Even then, if requested by an applicant, the Examiner must provide documentary evidence to support such assertions. The Examiner has not cited any art that demonstrates his assertion that the highly conserved polypeptides would not exhibit similar functions.

MPEP 2144.03:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, there is no evidence that the knowledge of the Examiner is such that official notice can be taken.

MPEP 2144.03 states:

> [A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the

> correctness of such assertions and allegations. **"The facts so noticed serve to `fill the gaps' which might exist in the evidentiary showing" and should not comprise the principle evidence upon which a rejection is based.**). See also In re Barr, 444 F.2d 588, 170 USPQ 330 (CCPA 1971) (scientific journal references were not used as a basis for taking judicial notice that controverted phrases were art-recognized because the court was not sure that the meaning of the term at issue was indisputable among reasonable men); and In re Eynde, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973) ("The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of [judicial] notice."

In this instance, the Examiner taking judicial notice provides the crux of the rejection, but no basis therefor is provided. In fact, the sequences of the encoded proteins are highly conserved such that there is no reason to conclude that one of skill in the art would not conclude that applicant did not have possession of the claimed genus at the time of filing.

The discussion in the previous responses and herein does indeed address this issue. The specification provides 56 species within the scope of the claims and teaches how to produce and test others. The encoded polypeptides are highly conserved, and as noted, substitution of the same mutation into each polypeptide renders them more conserved. There is nothing of record to suggest that the functioning of the Rep proteins among different serotypes, particularly those, now claimed, is different; and , in fact, the high conservation of sequence indicates otherwise. The attached alignments clearly demonstrate that these proteins are highly conserved and in fact are no more than allelic variants. Furthermore, the fact that the original amino acid at the initial position is different is not relevant to possession of the modified nucleic acid molecules.

35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 45, 46, 62, 70, 94 and 95 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for the full scope of the claims, because:

> the specification, while being enabling for a nucleic acid encoding a mutant form of Rep 78 or Rep 68 of AAV-2 (SEQ ID NO: 113), a cell comprising this nucleic acid, recombinant AAV-2 comprising this nucleic acid, and a cell comprising this recombinant AAV-2, does not reasonably provide enablement for a nucleic acid encoding an equivalent mutation in other AAV serotypes, Rep 52 or Rep 40 comprising this mutation, cells containing this nucleic, recombinant AAV comprising this nucleic acid, or cells comprising this recombinant AAV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
>
> The Examiner states:
>
> > There is no teaching in the specification and no suggestion in the art

> that a mutation at position 350 to N would necessarily function in the same regard as the T to N mutation exemplified in Rep 78 of AAV-2. The claims are broadly drawn as they encompass any of the versions of the rep protein derived from any of the AAV serotypes. The variation in the residue at position 350, and the apparently unknown function of Rep 52 and Rep 40 means that there is high degree of unpredictability in this regard. The specification exemplifies a T to N or at position 350 in Rep 78 of AAV-2. As argued above, there is no evidence that this would correlate to similar mutations in other serotypes. The specification makes no mention of the sequence differences at position 350 between the different serotypes, except for the alignment in Figure 3. There is no evidence of record that REP proteins from other serotypes bearing a mutation where the equivalent residue of 350 is mutated to N, would have a similar effect on viral titer. Thus to make any other serotype bearing a residue 350 to N mutation would require an undue level of experimentation. There is a high likelihood that no other serotype would result in the same phenotype as AAV-2, for the reasons delineated above and as such to make an AAV vector comprising this mutation in other serotypes would require the skilled artisan to identify other sites in a trial and error fashion. This constitutes an undue level of experimentation.

These assertions and the others proffered by the Examiner are discussed in turn below. This rejection respectfully is traversed.

Prior to analyzing the issues and address the Examiner's statements, it is noted (1) it is nucleic acid molecules that are claimed; (2) the function assessed is an increased viral titer of an AAV molecule whose genome includes such modification; (3) the fact that there is a different amino acid in one strain than the others, does not impact on enablement, since the claims are directed to the modified nucleic acid molecules; (4) the modified nucleic acid molecules encode proteins that are more similar to AAV-2 than dissimilar, since the modification results in the same amino acid at the locus; (5) the resulting proteins are highly conserved; and (6) as the Examiner notes that in the other AAV-serotypes the position is an A, and the instant application shows that replacement of A with N *results in increased titer.*

Relevant Law

To satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176

USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocchi *et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

First, it is noted the claims are directed to nucleic acid molecules encoding the Rep protein and that this mutation is mutation at a codon that is present in all of the overlapping proteins. Hence, when an AAV genome that includes a mutant Rep gene of the instant claims, all of the Rep proteins encoded by this gene will include this mutation. The instant application demonstrates that this mutation when introduced into an AAV genome gives rise to an increase in titer.

Enablement is a legal determination that assesses whether a specification teaches one of skill in the art to make and use what is claimed. Enablement is not precluded even if some experimentation is necessary, as long as the amount of experimentation is not undue. Atlas Powder Co. v. E. I. Du Pont De Nemours Co., 750 224 USPQ 409, 3 (Fed. Cir. 1984); W. L. Gore and Associates v. Inc., 721 220 USPQ 303, 315 (Fed. Cir. 1983).

Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 220, 223, 169 USPQ 367, 369 (CCPA 1971). An analysis of whether the rejected claims are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the claims as to teach one of skill in the art how to make and use what is claimed.

Notably, to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for what is claimed. In re Wright, 999 1557, 1561-62, 27 1510, 1513 (Fed. Cir. 1993). (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also Morehouse, 545 162, 192 USPQ 29 (CCPA 1976). The threshold step in resolving this issue is to determine whether the Examiner has met this burden of proof by advancing acceptable reasoning inconsistent with enablement. "Factors to be considered by the examiner in determining whether disclosure would require undue experimentation have been summarized in In re Wands, 858 731, 737, 8 1400, 1404, (Fed. Cir. 1988) and are outlined in the Guidelines and above. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the claimed subject matter, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. All factors must be considered. A deficiency in meeting one factor does not preclude a finding of enablement.

In this instance, the Examiner only urges that the specification does not teach that any change a position 350 would result in an increase in titer. The Examiner urges that the claims encompass all forms of Rep and all serotypes. The Examiner states that the specification makes no mention of mutations in other serotypes "except for the alignment in Figure 3." In focusing on only one factor, the alleged deficiencies in the teachings of the specification, the Examiner has failed to set forth a *prima facie* case of lack of enablement.

Addressing the points, the so-called alignment in Figure 3, provides mutated Rep proteins from the seven serotypes. The mutated proteins are presented as an alignment to demonstrate that similarity and high conservation among this protein in the various serotypes. Furthermore, the attachment below, indicates that the serotypes as claimed are highly conserved. There is no evidence of record to suggest that AAV genomes of such highly conserved serotypes containing mutations that encode such polypeptides would not produce higher titers of virus when expressed in a host. There is no evidence of record that Rep proteins differ among the different serotypes, and the evidence of record is to the contrary.

The nucleic acid sequences of the genomes of the various AAV serotypes (AAV-1, -2, -3, -3B, -4, -5, -6 and -7) are provided (see, *e.g.*, SEQ ID Nos. 736-748), with the location of the Rep78 noted.. It requires no experimentation to modify the sequence each of the genomes as claimed in claims 62 and 96-100. One merely has to change the codon at the indicated locus. The specification, as discussed below, provides method for producing additional mutations and testing them to identify any others that increase titer. Hence the specification provides 56 examples, a method for identifying other mutations and assays for testing them.

With respect to the statement that there are three types of Rep proteins, these proteins are encoded by overlapping reading frames, and they are only shifted at the 5' terminus. In the region of overlap, a mutation in one protein is a mutation in all proteins. The instant claims are directed to *nucleic acid molecules encoding mutated proteins* and specify the location of the mutation with reference to Rep78, which begins at the first codon. A mutation in a locus of overlap, is a mutation in all three Rep proteins. It does not make sense to discuss the mutations separately. An AAV genome cannot encode a mutant Rep 78 and not also encode mutant Rep 52 and Rep 40, unless the mutation is in the 5' region that extends beyond the terminus of one or both of Rep 52 and/or Rep 40.

Application of the Factors Enumerated in In re Wands

Turning to a consideration of the factors, it respectfully is submitted that it would not requirement undue experimentation to make and use the claimed subject matter.

1) The scope of the claims

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity. Increased activity of the Rep protein as defined by the specification and claim is "manifested as an increased titer of virus upon introduction and replication in a host cell of virus, in its genome, containing the nucleic acid molecule

encoding the mutant Rep protein compared titer of virus upon introduction and replication of a virus containing a wild type Rep gene."

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies specific amino acid replacements in the mutant Rep protein.

Claims 96 and 97 specify the encoded Rep proteins; and claims 98-100 are directed to nucleic acid that constitutes he modified AAV genomes.

2) The level of skill in the art

The level of skill in this art is recognized to be high as and is evidenced by the literature in the area authored by and directed towards scientists with advanced degrees.

3) Teachings in the specification and predictability

The specification describes 56 polypeptides and by extension nucleic acid molecules that when included in an AAV genome result in increased viral titer. The specification provides data for 8 such polypeptides. The specification also demonstrates the conservation among the Rep78 and genomes of all AAV serotypes and also describes that the Rep proteins are encoded by overlapping genes. The attachment (from FIGS 3A and 3B) shows that the AAV serotypes as presently claimed encode highly conserved proteins; most of the sequences are either identical or differ only by one conservative amino acid.

In addition, the specification provides a detailed description and exemplification of application of method for generating mutant polypeptides and AAV genomes that result in increased viral titer. The method, which is non-random, is described in great detail, and includes assays for identifying whether a particular mutation. Application of the method will result in identification of viral genomes that contain a mutation in the Rep gene(s) that exhibit increased titer. Application of the method will result in AAV genomes (and hence nucleic acid molecules encoding REP proteins and the encoded proteins) that have a mutation in the Rep gene(s) that results in increased viral titer. While not every mutation results in such increase, the method is designed to produce those that do have the desired property. Hence, while it is not necessarily 100% predictable whether a particular mutation will result in a change in titer, it is 100% predictable that application of the method will produce AAV genomes with such a mutation.

The specification exemplifies all Rep78 proteins within the scope of claim 62. By virtue of disclosure of the proteins, discloses nucleic acid encoding these proteins, and necessarily the corresponding Rep 52 and Rep 40 proteins.

4) Knowledge of the those of skill in the art

As described in the specification, a great deal is known about AAV biology and at least 7 serotypes and their genomes have been extensively studied and characterized. The instant application provides a new class (genus) of mutations, but the genome and the encoded proteins are well studied and known. Those of skill in the art recognize the high conservation among these serotypes. For example, AAV2, AAV3, and AAV6 are 82% identical at the nucleic acid sequence level; and AAV4 is 75-78% identical to these serotypes; and AAV3b is virtually identical AAV3; AAV6 is a variant of AAV1 (see, *e.g.*, Rutledge *et al.* (1998) *J. Virol. 72*:309-319).

5) Working Examples

The specification provides numerous working examples as discussed throughout this response and specifically demonstrates 8 different mutations in the AAV-2 serotypes that exhibit the requisite activity. In addition, as discussed in detail above, the specification provides the corresponding mutation in all other serotypes.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable with 100% that application of the methods described and provided in the specification results in nucleic acid molecules and AAV genomes that have mutations in the Rep gene(s) and exhibit an increased titer, and the breadth of the claims, it would not require undue experimentation for one of skill in the art to prepare a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity, where increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene.

The Examiner has not established that the combination these elements is insufficient to make and use nucleic acid molecules within the scope of the claims. The test [for enablement]is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (Bd Pat App Int. 1982). In this

instance, the specification provides detailed guidance for isolation and testing of molecules to identify those that possess the requisite activity as well as numerous working examples.

Rebuttal to Examiner's arguments:

> **1.** It is acknowledged that page 19 of the 1/5/06 amendment does indeed address certain points of the rejection. First, the second full paragraph of page 19 alleges that Figure 3 does not show an alignment. Contrary to this page 5, line 25 of the specification states, "FIGURES 3A and 38 show the alignment of amino acid sequences of Rep78". Indeed, however, Applicant supports Examiner's position that it would seem highly unlikely that a position 350 to N mutation the other serotypes aside from the exemplified AAV-2 would result in an alteration in titer. The rejection clearly states that due to the lack of any difference in titer among different serotypes one would not have identified position 350 by alanine scanning. With no difference in titer it calls into question the whether this position plays a critical role in viral titer.

As discussed above, it does not matter whether the position "would have been identified by Alanine scanning" in other serotypes. The position has been identified and is taught in the specification; there is no need to identify this position again. The method provided in the specification identified 8 modifications; it would be possible to apply this method to other serotypes and identify additional mutations that give rise to increased titers.

The Examiner has provided no reasoning to support his assertion that "a position 350 to N mutation the other serotypes aside from the exemplified AAV-2 would result in an alteration in titer." As discussed above, the Examiner must provide a basis for such supposition and cannot take judicial notice of such fact. The specification teaches the opposite, that an N at the 350 locus results in an increased titer. In view of the high conservation among the encoded proteins, such mutation renders the proteins more similar. The Examiner, in fact, has pointed out an argument why such mutation results in higher titer in the other serotypes. As shown in the specification, an A to N modification in AAV-2 results in increased titer. Hence, in the similar serotypes, the same change would have the same effect.

> **2.** In the next paragraph Applicant states that because the Rep proteins share coding sequence it is improper to consider them individually. This is incorrect, as despite the fact that the different forms of the Rep protein do indeed share the same reading frame, the fact the claims are treating the different Rep protein individually means the rejection must address the individual proteins. As presently drawn the claims are drawn to individual Rep proteins. It is well within the level of ordinary skill in the art to express only a single form of the Rep proteins. The claims encompass this possibility. The rejection addresses the fact that there is no reason to believe

that either of Rep 52 or Rep 40 alone would lead to the effects on viral titer if expressed individually in the context of an infection, for example through exogenous expression form a plasmid. It is for this reasons that the rejection is made specifically pointing out the apparent inability of Rep 52 or Rep 40 to result in the desired phenotype of an increase titer.

The Examiner is begging the question, since the property assessed is increased viral titer of an AAV whose genome includes a modification. To assess it, the modified nucleic acid molecule must be introduced into the viral genome. Once introduced, it is irrelevant which protein results in the desired effect. Furthermore, as noted, the claims are directed to nucleic acid molecules; a modification in the nucleic acid molecule results in a modification of all of the proteins that are encoded by the modified region. There is no evidence of record that Rep 52 or Rep 40 are unable to alter the phenotype of an increase in titer. Rep 52 is encoded by nucleotides 993-2,186; and Rep 40 is encoded by amino acids 993-1906. Some or all of the identified modifications are encoded by nucleic acid molecules that result in modified Rep52 and modified Rep40. Hence the Examiner's statement is without basis.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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17109-003001/ 37851-912

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Attachment
A

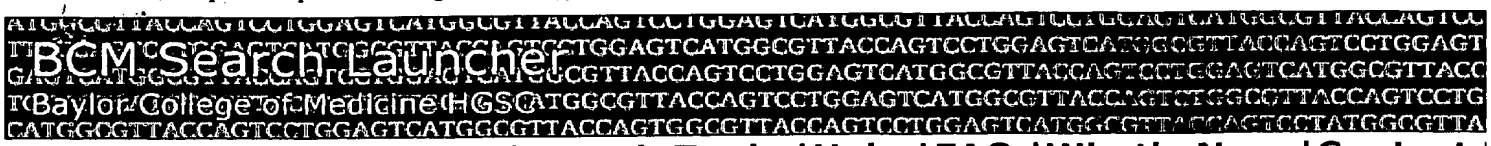
```
          10         20         30         40         50         60
1  MPGFYEIVIKVPSDLDEHLPGISDSFVSWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQ   60
2  MPGFYEIVIKVPSDLDEHLPGISDSFVNWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQ   60
3  MPGFYEIVLKVPSDLDEHLPGISNSFVNWVAEKEWELPPDSDMDPNLIEQAPLTVAEKLQ   60
4  MPGFYEIVLKVPSDLDEHLPGISNSFVNWVAEKEWELPPDSDMDPNLIEQAPLTVAEKLQ   60
5  MPGFYEIVLKVPSDLDEHLPGISDSFVSWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQ   60
6  MPGFYEIVIKVPSDLDGHLPGISDSFVNWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQ   60
C  MPGFYEIV#KVPSDLDGHLPGIS#SFV*WVAEKEWELPPDSDMDLNLIEQAP6TVAEKLQ
          70         80         90        100        110        120
1  RDFLVQWRRVSKAPEALFFVQFEKGESYFHLHILVETTGVKSMVLGRFLSQIRDKLVQTI  120
2  RDFLVQWRRVSKAPEALFFVQFEKGESYFHLHILVETTGVKSMVLGRFLSQIRDKLVQTI  120
3  REFLVEWRRVSKAPEALFFVQFEKGETYFHLHVLIETIGVKSMVVGRYVSQIKEKLVTRI  120
4  REFLVEWRRVSKAPEALFFVQFEKGETYFHLHVLIETIGVKSMVVGRYVSQIKEKLVTRI  120
5  REFLVEWRRVSKAPEALFFVQFEKGDSYFHLHILVETVGVKSMVVGRYVSQIKEKLVTRI  120
6  RDFLTEWRRVSKAPEALFFVQFEKGESYFHMHVLVETTGVKSMVLGRFLSQIREKLIQRI  120
C  RDFLT#WRRVSKAPEALFFVQFEKG##YFH#H#L#ET#GVKSMV#GR##SQI###L#**I
         130        140        150        160        170        180
1  YRGIEPTLPNWFAVTKTRNGAGGGNKVVDECYIPNYLLPKTQPELQWAWTNMEEYISACL  180
2  YRGIEPTLPNWFAVTKTRNGAGGGNKVVDECYIPNYLLPKTQPELQWAWTNMEEYISACL  180
3  YRGVEPQLPNWFAVTKTRNGAGGGNKVVDDCYIPNYLLPKTQPELQWAWTNMDQYLSACL  180
4  YRGVEPQLPNWFAVTKTRNGAGGGNKVVDDCYIPNYLLPKTQPELQWAWTNMDQYLSACL  180
5  YRGVEPQLPNWFAVTKTRNGAGGGNKVVDDCYIPNYLLPKTQPELQWAWTNMDQYISACL  180
6  YRGIEPTLPNWFAVTKTRNGAGGGNKVVDECYIPNYLLPKTQPELQWAWTNMEQYLSACL  180
C  YRG#EP*LPVWFAVTKTRNGAGGGNKVVD#CYIPNYLLPKTQPELQWAWTNM##Y#SACL
         190        200        210        220        230        240
1  NLAERKRLVAQHLTHVSQTQEQNKENLNPNSDAPVIRSKTSARYMELVGWLVDRGITSEK  240
2  NLAERKRLVAHDLTHVSQTQEQNKENLNPNSDAPVIRSKTSARYMELVGWLVDRGITSEK  240
3  NLAERKRLVAQHLTHVSQTQEQNKENQNPNSDAPVIRSKTSARYMELVGWLVDRGITSEK  240
4  NLAERKRLVAQHLTHVSQTQEQNKENQNPNSDAPVIRSKTSARYMELVGWLVDRGITSEK  240
5  NLAERKRLVAQHLTHVSQTQEQNKENQNPNSDAPVIRSKTSARYMELVGWLVDRGITSEK  240
6  NLTERKRLVAQHLTHVSQTQEQNKENQNPNSDAPVIRSKTSARYMELVGWLVDKGITSEK  240
C  NL*ERKRLVAAHLTHVSQTQEQNKENQNPNSDAPVIRSKTSARYMELVGWLVD#GITSEK
         250        260        270        280        290        300
1  QWIQEDQASYISFNAASNSRSQIKAALDNAGKIMALTKSAPDYLVGPAPPADIKTNRIYR  300
2  QWIQEDQASYISFNAASNSRSQIKAALDNAGKIMALTKSAPDYLVGPAPPADIKTNRIYR  300
3  QWIQEDQASYISFNAASNSRSQIKAALDNASKIMSLTKTAPDYLVGSNPPEDITKNRIYQ  300
4  QWIQEDQASYISFNAASNSRSQIKAALDNASKIMSLTKTAPDYLVGSNPPEDITKNRIYQ  300
5  QWIQEDQASYISFNAASNSRSQIKAALDNASKIMSLTKTAPDYLVGQNPPEDISSNRIYR  300
6  QWIQEDQASYISFNAASNSRSQIKAALDNAGKIMSLTKTAPDYLVGQQPVEDISSNRIYK  300
C  QWIQEDQASYISFNAASNSRSQIKAALDNA#KIM#LTK*APDYLVG#*P**DI##NRIY#
         310        320        330        340        350        360
1  ILELNGYEPAYAGSVFLGWAQKRFGKRNTIWLFGPATTGKTNIAEAIAHAVPFYGCVNWT  360
2  ILELNGYDPAYAGSVFLGWAQKRFGKRNTIWLFGPATTGKTNIAEAIAHAVPFYGCVNWT  360
3  ILELNGYDPQYAASVFLGWAQKKFGKRNTIWLFGPATTGKTNIAEAIAHAVPFYGCVNWT  360
4  ILELNGYDPQYAASVFLGWAQKKFGKRNTIWLFGPATTGKTNIAEAIAHAVPFYGCVNWT  360
5  ILEMNGYDPQYAASVFLGWAQKKFGKRNTIWLFGPATTGKTNIAEAIAHAVPFYGCVNWT  360
6  ILELNGYDPQYAASVFLGWATKKFGKRNTIWLFGPATTGKTNIAEAIAHTVPFYGCVNWT  360
C  ILE#NGY#P*YA#SVFLGWA#K#FGKRNTIWLFGPATTGKTNIAEAIAH*VPFYGCVNWT
```

Attachment
B

```
          370        380        390        400        410        420
1  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS  420
2  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS  420
3  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIEPTPVIVTS  420
4  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIEPTPVIVTS  420
5  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS  420
6  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS  420
C  NENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQI#PTPVIVTS
          430        440        450        460        470        480
1  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLEHDFGKVTKQEVKEFFRWAQDHVTEV  480
2  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLEHDFGKVTKQEVKEFFRWAQDHVTEV  480
3  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWASDHVTDV  480
4  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWASDHVTDV  480
5  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTKRLEHDFGKVTKQEVKDFFRWASDHVTEV  480
6  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWAKDHVVEV  480
C  NTNMCAVIDGNSTTFEHQQPLQDRMFKFELT#RL#HDFGKVTKQEVK#FFRWA*DHV*VV
            490        500                                  510        520
1  AHEFYVRKGGANKRPAPDDADKSEPKRA------------------CPSVADPSTSDAEG  522
2  AHEFYVRKGGANKRPAPDDADKSEPKRA------------------CPSVADPSTSDAEG  522
3  AHEFYVRKGGAKKRPASNDADVSEPKRQ------------------CTSLAQPTTSDAEA  522
4  AHEFYVRKGGAKKRPASNDADVSEPKRQ------------------CTSLAQPTTSDAEA  522
5  THEFYVRKGGARKRPAPNDADISEPKRA------------------CPSVAQPSTSDAEA  522
6  EHEFYVKKGGAKKRPAPSDADISEPKRV------------------RESVAQPSTSDAEA  522
C  *HEFYV#KGGA#KRPA**DAD*SEPKR*                    #*S*A#P#TSDAE#
         530        540        550        560        570        580
1  APVDFADRYQNKCSRHAGMLQMLFPCKTCERMNQNFNICFTHGTRDCSECFP--GVSESQ  580
2  APVDFADRYQNKCSRHAGMLQMLFPCKTCERMNQNFNICFTHGTRDCSECFP--GVSESQ  580
3  P-ADYADRYQNKCSRHVGMNLMLFPCKTCERMNQISNVCFTHGQRDCGECFPGMSESQPV  581
4  P-ADYADRYQNKCSRHVGMNLMLFPCKTCERMNQISNVCFTHGQRDCGECFPGMSESQPV  581
5  P-VDYADRYQNKCSRHVGMNLMLFPCRQCERMNQNVDICFTHGVMDCAECFP-VSESQPV  580
6  S-INYADRYQNKCSRHVGMNLMLFPCRQCERMNQNSNICFTHGQKDCLECFP-VSESQP   579
C  ***##ADRYQNKCSRH*GM**MLFPCR*CERMNQ#*##CFTHG**DC*ECFp****S#**
            590        600        610        620
1  PVVRKRTYRKLCAIHHLLGRAPEIACSACDLVNVDLDDCVSEQ                   623
2  PVVRKRTYRKLCAIHHLLGRAPEIACSACDLVNVDLDDCVSEQ                   623
3  SVVKKKTYQKLCPIHHILGRAPEIACSACDLANVDLDDCVSEQ                   624
4  SVVKKKTYQKLCPIHHILGRAPEIACSACDLANVDLDDCVSEQ                   624
5  SVVRKRTYQKLCPIHHIMGRAPEVACSACELANVDLDDCDMEQ                   623
6  VSVVKKAYQKLCYIHHIMG-KVPDACTACDLVNVDLDDCIFEQ                   621
C  **V#K#*Y#KLC*IHHIMGR*****C#AC#L*NVDLDDC**EQ
```

Attachment C

Printout from ClustalW Protein Sequence Parameters



ClustalW Multiple Sequence Alignment (@BCM)

Cut and paste sequences here (ReadSeq formats accepted;
All sequences must be in the same format type; max 20,000 chars, total):

Perform Search Clear Input

DNA Sequence Parameters:

Fast Pairwise Alignment Parameters:

K-tuple (word) size: 2
Window size: 4
Scoring method: Percentage
Number of top diagonals: 4
Gap penalty: 5

Multiple Alignment Parameters:

Gap opening penalty: 10.0
Gap extension penalty: 5.0
Weight transitions: Yes

Protein Sequence Parameters:

Fast Pairwise Alignment Parameters:

K-tuple (word) size: 1
Window size: 5
Scoring method: Percentage
Number of top diagonals: 5
Gap penalty: 3

Multiple Alignment Parameters:

Weight matrix: blosum

ATTACHMENT C

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Gap opening penalty: 10.0
Gap extension penalty: 0.1
Hydrophilic gaps: On
Hydrophilic residues: GPSNDQERK
Residue-specific gap penalties: On

Other Parameters:

Quicktree (always On): On
Divergence cutoff (% identity for delay): 40
Gap separation distance: 8
End gap separation penalty: Off
Output order: aligned

Credits:
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ClustalW Server @BCM: *Kim C. Worley, Michael P. McLeod and Zhenwu Yang, Human Genome Center, Bay of Medicine (Email)*

Last change: Tue Apr 9 14:06:51 CDT 1996